The Pharmaceutical and Chemical Journal, 2018, 5(1):163-173

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Design, Formulation and Evaluation of Fast Disintegrating Tablets of Febuxostat

Akanksha Sharma[1], Vishal Garg[2], Manish Kumar Gupta[1], Vijay Sharma[1]

[1]Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India
[2]Jaipur School of Pharmacy, Maharaj Vinayak Global University, Jaipur Rajasthan, India

Abstract Febuxostat, is a medication used in the treatment of chronic gout and hyperuricemia. Febuxostat is a non-purine xanthine oxidase. It is a BCS class II drug. It exhibits poor bioavailability about 49% which is attributed to its poor bioavailability and poor solubility. The present work was aimed to overcome its limitation of poor solubility. Drug and beta cyclodextrin complexes were prepared in the ratio 1:1 and 1:2. Studies show that solubility was better for 1:2 ratio (855.20 µg/ml) as compared to that of pure drug (10.50 µg/ml). Tablets were prepared by using ingredients such as Beta-Cyclodextrin, Crospovidone, Locust Bean Gum, Crosscarmellose, Microcrystalline Cellulose, Mannitol, Magnesium Stereate, Sodium Saccharine.

Keywords Febuxostat, Beta-Cyclodextrin, Crospovidone, Locust Bean Gum, Crosscarmellose

Introduction

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of their ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance of tablets [1-4]. Fast disintegrating tablets (FDTs) are not only preferable for people who have swallowing difficulties, but also are ideal for active people. Fast disintegrating drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time offer added advantages over both the traditional dosage forms. The Fast Disintegrating Tablet (FDT) is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and/or quick disintegrating tablet [7-12].

The purpose of the present investigation was to prepare fast disintegrating tablet of febuxostat, using different superdisintegrants by increasing the solubility and dissolution rate of model drug by the preparation of its solid dispersion with Beta-Cyclo Dextrin using kneading method.

Drug Profile of Febuxostat

Chemical Structure:

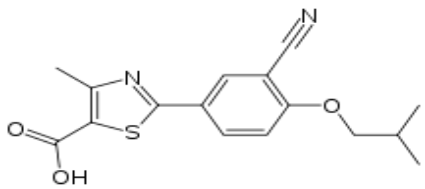

Figure 1: Structure of Febuxostat

Category : Xanthine oxidase inhibitor, Hyperureceimc, Antigout agent.
pka : 7.7
Solubility : It is freely soluble in dimethylforamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile and practically insoluble in water.
Half life : 5-8 hrs [13]

Experimental Work

Materials

Febuxostat was obtained from Emcure Pharmaceuticals, Pune. Beta-Cyclodextrin from SD Fine Chem. Ltd., Mumbai, Crospovidone from BASF and Locust Bean Gum (LBG) from Tropolites Foods Pvt. Ltd., Gwalior. All other chemicals and solvent used were of pharmaceutical and analytical grade.

Pre Formulation Studies

1. Swelling Index of Superdisintegrants were found as follows:

Table 1: Swelling index of different superdisintegrants

S.No	Name of the Superdisintegrant	Swelling Index* (%v/v)
1	Crosspovidone	93.34±2.35
2	Locust Bean Gum	121.68±2.35
3	Croscarmellose	75.01±4.08

*Data expressed as mean ± S D (n=3)

2. **Physical Appearance**

Sample of Febuxostat was observed to be white to off white powder.

3. **Melting Point Determination**

Melting point of 205˚C was observed which was in accordance with the literature value and was also confirmed by DSC (Fig 2). This confirms the authenticity and purity of the drug.

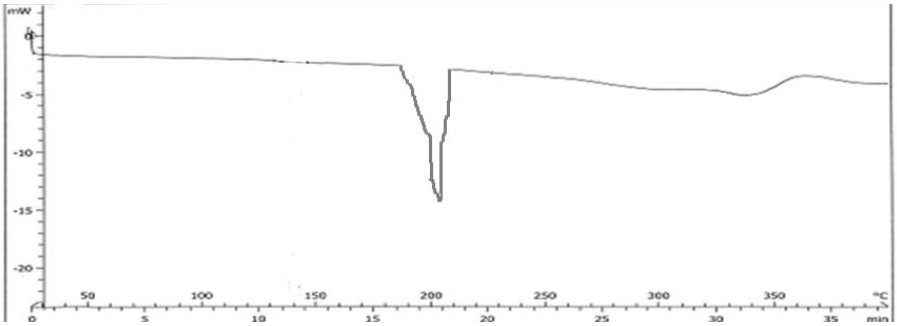

Figure 2: DSC curve of pure febuxostat

4. **Calibration Curves:**

Preparation of Calibration Curve in Methanol

The absorption maximum (λ_{max}) of febuxostat was found to be 315nm and the spectrum has been shown (Fig 3)

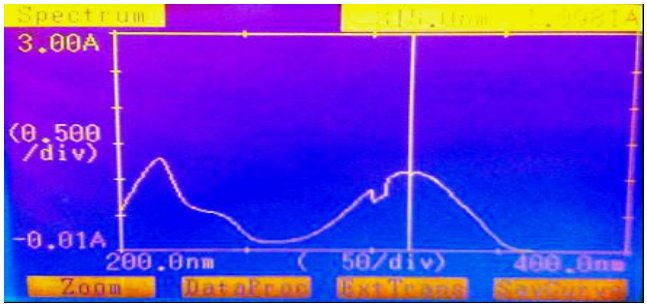

Figure 3: UV spectrum of 10 µg/ml solution of febuxostat in methanol

Table 2: Calibration data of febuxostat in methanol

Concentration (µg/ml)	Mean Absorbance* ± SD
2	0.272±0.006
4	0.421±0.002
6	0.581±0.001
8	0.778±0.002
10	0.92±0.002
12	0.962±0.005

Data are expressed as mean ± S.D (n=3)

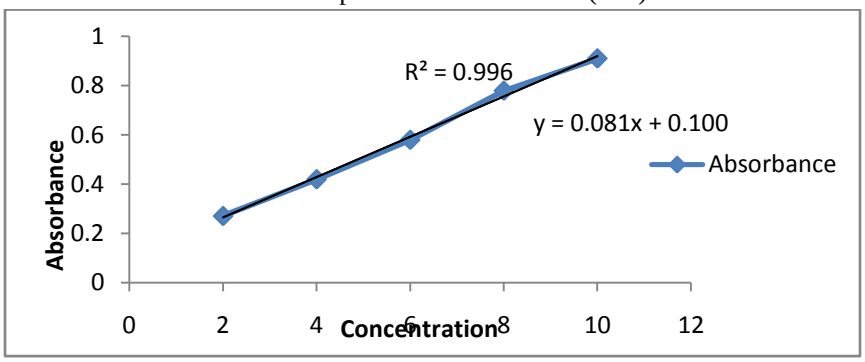

Figure 4: Standard curve of febuxostat in methanol

Preparation of Calibration Curve in 0.05 M Phosphate Buffer (pH 6.0)

a) Preparation of 0.05M Phosphate Buffer (pH 6.0)

The absorption maximum (λ_{max}) of febuxostat in phosphate buffer (pH 6.0) was found to be 315 nm and the spectrum has been shown in Fig. 5.

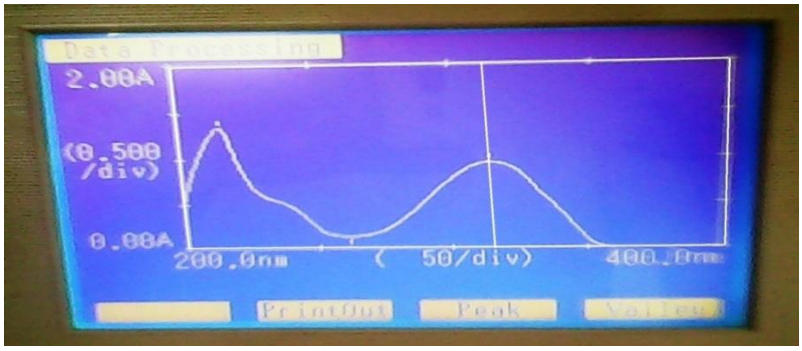

Figure 5: UV spectrum of 10 µg/ml solution of febuxostat in 0.05 M phosphate buffer (pH 6.0)

b) Preparation of Calibration Curve

The calibration curve of febuxostat was found to be linear in the phosphate buffer (pH 6.0). The absorbance of febuxostat is shown in table 3 and graph is represented in fig 6.

Table 3: Calibration data of febuxostat in phosphate buffer pH 6.0

Concentration (µg/ml)	Mean Absorbance* ± SD
2	0.177±0.002
4	0.341±0.006
6	0.495±0.007
8	0.643±0.009
10	0.782±0.001
12	0.924±0.009

Data are expressed as mean ± S.D (n=3)

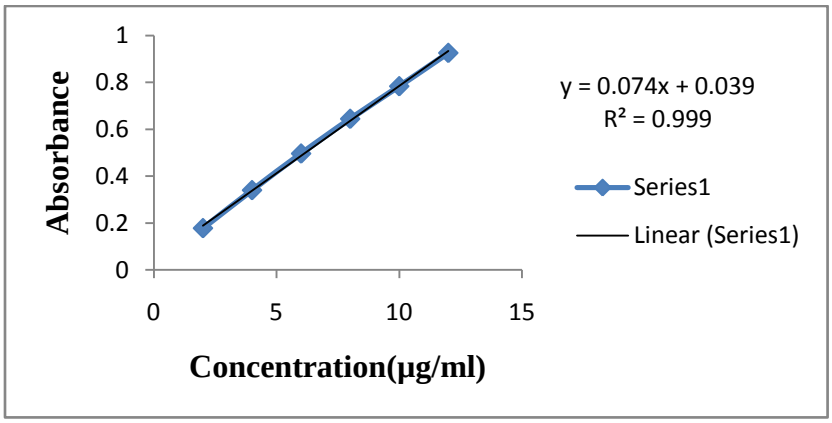

Figure 6: Standard curve of febuxostat in phosphate buffer pH 6.0

5. Drug Excipient Compatibility Study

Drug excipient studies showed that there was no discoloration, liquefaction and clump formation between drug and polymer physical mixtures. This indicates that there was no physical interaction between drug and the polymer used. No significant shift in the peak was observed which revealed that both the drug and polymer are compatible with each other. Data is as under:

Table 4: Drug Excipient Compatibility Study Data

Mixture	Week 1 Physical changes	Week 2 Physical changes	Week 3 Physical changes	Week 4 Physical changes	FTIR peaks (cm^{-1})
Drug	**NC**	**NC**	**NC**	**NC**	3744.56, 2976.54, 2363.08, 1693.29, 1515.45
Drug + LBG	**NC**	**NC**	**NC**	**NC**	3744.69, 2976.49, 2363.55, 1698.74 1514.96
Drug + Crospovidone	**NC**	**NC**	**NC**	**NC**	3744.42 2976.74, 2362.37, 1739.57, 1516.10
Drug + Croscarmellose Sodium	**NC**	**NC**	**NC**	**NC**	3744.55, 2976.36, 2362.67, 1741.57, 1514.10

NC: No Change

6. Preparation of Solid Dispersions of Febuxostat

Physical mixtures were prepared of febuxostat with Beta-Cyclodextrin in ratios i.e. 1:1 and 1:2. Formulation numbers were kept as SD1 and SD2 respectively.

7. Characterization of Solid Dispersions

Solubility Studies

Solubility data of pure drug and solid dispersions in phosphate buffer (pH 6.0) at 37±2 ˚C were shown in table 5 and graph is represented in Fig. 7.

Table 5: Solubility data of pure drug and solid dispersions in phosphate buffer (pH 6.0) at 37±2 ˚C

Formulation Number	Solubility (µg/ml)
Pure drug	10.50±0.001
SD1	435.00±0.006
SD2	855.20±0.006

Data are expressed as mean ± S.D. (n = 3)

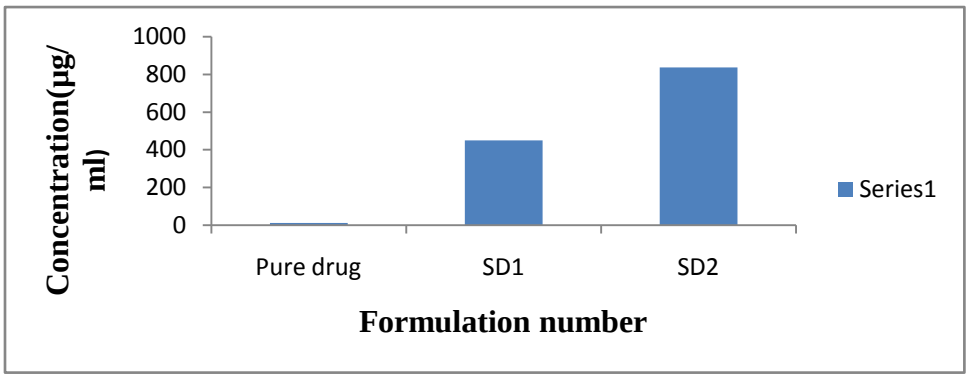

Figure 7: Solubility plot of pure drug and solid dispersions at 37±2 ˚C

***In vitro* Drug Release**

The dissolution profile of pure drug and solid dispersions were carried out in phosphate buffer (pH 6.0). Dissolution release values are shown in Table 6.

Table 6: Dissolution release profile of pure drug and solid dispersions

Time (min)	Pure drug	SD1	SD2
0	0	0	0
5	6.20	26.44	35.47
10	9.74	28.92	46.14
15	11.62	30.58	61.54
20	16.31	35.33	67.14
25	19.30	46.14	74.25
30	22.45	52.64	82.00

Data are as mean±expressed S.D. (n=3)

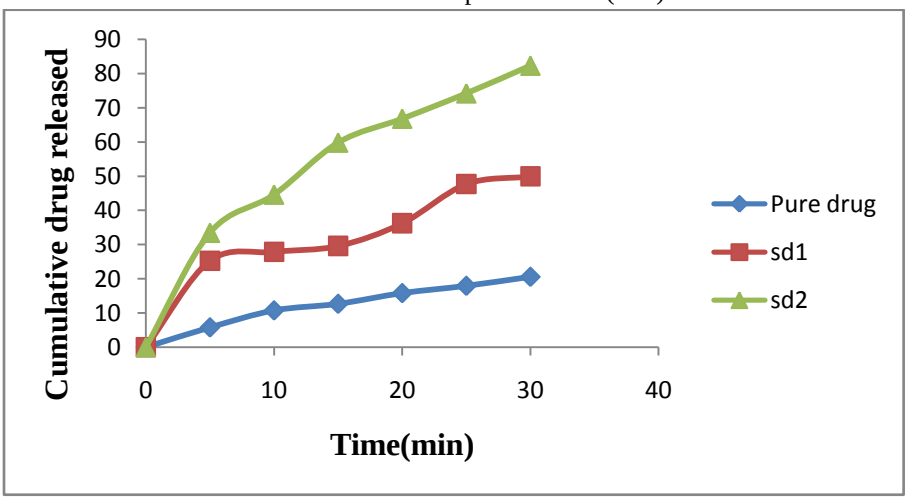

Figure 8: Percent release of pure drug and solid dispersions

8. FT-IR Studies

The FT-IR has been employed as a useful tool to identify the drug excipient intraction. Samples were analyzed by potassium bromide pellet method in an IR Spectrophotometer in the region between 4000 to 400cm^{-1}.

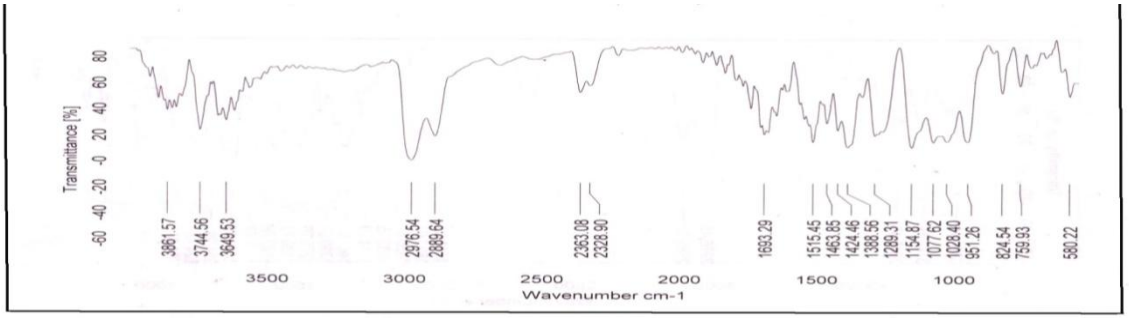

Figure 9: IR spectra of pure febuxostat

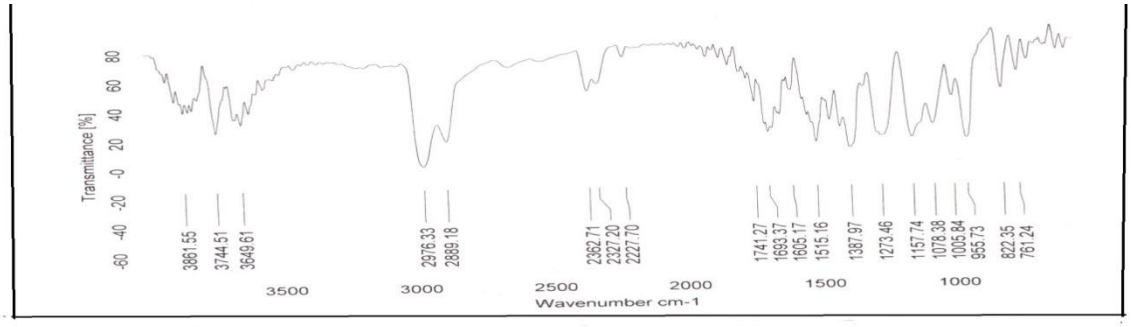

Figure 10: IR spectra of solid dispersion (SD2)

9. Differential Scanning Colorimetry (DSC) Analysis

Differential Scanning Colorimetry was performed on a METTLER DSC 30. The samples analyzed by heating at scanning rate of 20 ºC/minute over a temperature range 25ºC to 300 ºC.

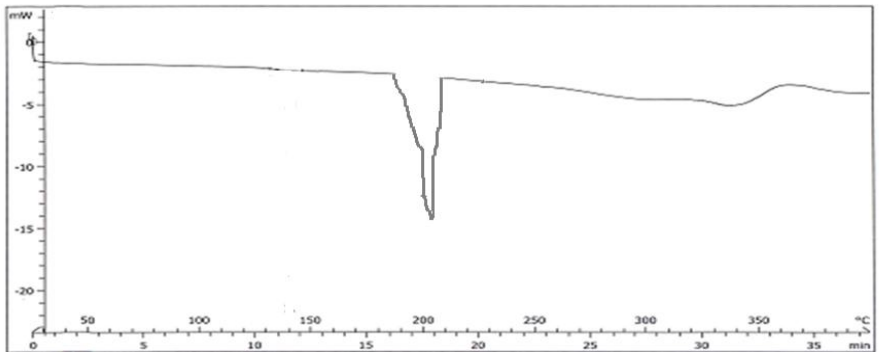

Figure 11: DSC curve of pure febuxostat

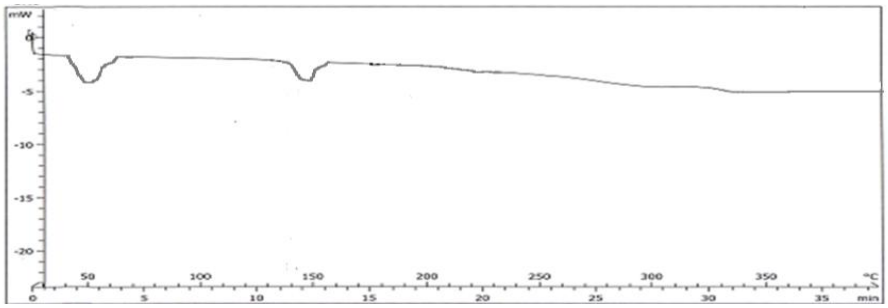

Figure 12: DSC curve of β-CD

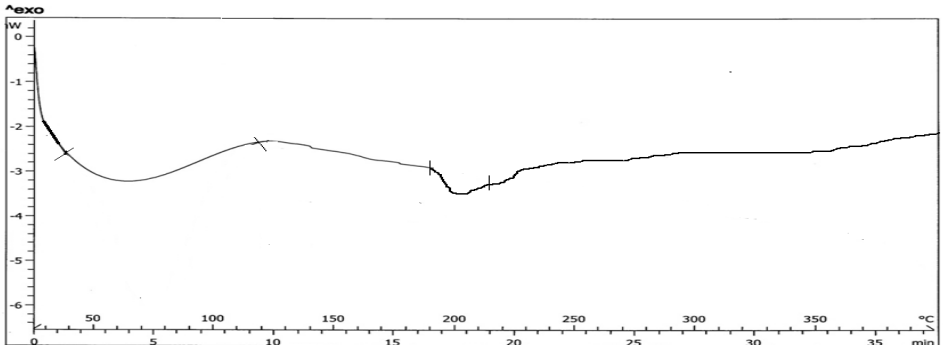

Figure 13: DSC curve of Solid Dispersion of Febuxostat with β-CD solid dispersion in ratio 1:2

10. Manufacturing Process

Febuxostat and β-CD was sifted through Sieve No. 40. Febuxostat and β-CD solid dispersion were prepared by well mixing both in RMG and added water with kneading for 2 min then kept under kneading for 1 hr. Complex was dried in Retech dryer until LOD reached below 2 %. Passed the complex through Sieve No. 30 and mixed previously sifted superdisintegrant, mannitol, sodium saccharine and Avicel PH 102 through Sieve No. 40 and mixed in octagonal blender for 30 min. Added previously sifted magnesium stearate in above mixture and mixed the blend for 5 min. Finally, lubricated blend compressed with 9.0 mm punch. The superdisintegrants i.e. crospovidone, CCM and LBG were in varying concentration (4, 6 and 8 % w/w)

Table 7: Formulation of preliminary trial batches

Ingredients (mg)	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6	FDT7	FDT8	FDT9
Drug : β-CD complex	120	120	120	120	120	120	120	120	120
LBG	10	15	20	-	-	-	-	-	-
Crosspovidone	-	-	-	10	15	20	-	-	-
CCS	-	-	-	-	-	-	10	15	20
MCC	50	50	50	50	50	50	50	50	50
Mannitol	62.25	57.25	52.25	62.25	57.25	52.25	62.25	57.25	52.25
Sodium Saccharine	4	4	4	4	4	4	4	4	4
Magnesium Stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight(mg)	250	250	250	250	250	250	250	250	250

MCC: Microcrystalline Cellulose, CCS: Croscarmellose Sodium, LBG: Locust Bean Gum

Results and Discussions

Characterization of Blends

Table 8: Characterization of blends (Pre-compression Parameters)

Formulation codes	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose
FDT-1 (4%)	0.405±0.003	0.462±0.002	1.140±0.015	12.33±1.271	27.33±0.608
FDT-2 (6%)	0.417±0.004	0.479±0.004	1.148±0.012	12.94±0.855	26.52±1.031
FDT-3 (8%)	0.422±0.003	0.485±0.004	1.149±0.014	12.989±0.995	25.77±0.996
FDT-4 (4%)	0.398±0.001	0.457±0.003	1.148±0.015	12.91±1.298	31.20±0.697
FDT-5 (6%)	0.402±0.002	0.462±0.001	1.149±0.002	12.98±0.065	28.14±0.536
FDT-6 (8%)	0.392±0.001	0.454±0.004	1.158±0.012	13.65±0.832	28.56±1.638
FDT-7 (4%)	0.412±0.003	0.482±0.004	1.169±0.006	14.52±0.536	33.04±1.004
FDT-8 (6%)	0.419±0.004	0.492±0.002	1.174±0.002	14.83±0.074	31.59±0.907
FDT-9 (8%)	0.415±0.003	0.489±0.004	1.178±0.012	15.13±0.816	30.39±0.501

Data are expressed as mean ± S.D. (n = 3)

Table 9: Characterization of fast disintegrating tablets (Post-compression parameters)

Formulation Codes	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
FDT-1 (4%)	248.4±1.54	3.02±0.184	4.74±0.069	0.18
FDT-2 (6%)	249.7±1.45	3.05±0.092	5.24±0.058	0.24
FDT-3 (8%)	250.6±2.05	3.01±0.050	5.41±0.100	0.25
FDT-4 (4%)	250.3±2.54	3.04±0.064	4.62±0.111	0.18
FDT-5 (6%)	249.6±1.90	3.07±0.084	4.85±0.090	0.26
FDT-6 (8%)	251.4±1.84	3.06±0.067	4.98±0.090	0.24
FDT-7 (4%)	250.7±1.64	3.04±0.062	5.24±0.094	0.21
FDT-8 (6%)	249.7±1.41	3.03±0.040	5.17±0.094	0.16
FDT-9 (8%)	248.5±1.41	3.10±0.052	4.85±0.095	0.22

Data are expressed as mean ± S.D. (n = 3)

Table 10: Characterization of fast disintegrating tablets

Formulation Codes	Wetting Time (sec)	Disintegration Time(sec)	Drug Content (%)
FDT-1 (4%)	150.00±0.61	165.00±0.52	98.64±0.52
FDT-2 (6%)	105.20±0.37	110.40±1.28	102.08±0.88
FDT-3 (8%)	62.54±2.17	69.53±2.01	100.33±0.57
FDT-4 (4%)	83.13±0.84	93.10±2.55	99.43±0.84
FDT-5 (6%)	59.10±2.20	66.41±2.15	98.85±0.73
FDT-6 (8%)	40.30±1.40	51.64±1.19	100.41±0.21
FDT-7 (4%)	45.30±1.21	62.13±0.67	99.68±0.33
FDT-8 (6%)	25.41±1.41	31.41±1.45	100.50±0.43
FDT-9 (8%)	23.10±0.84	28.47±1.14	101.01±0.77

Data are expressed as mean ± S.D. (n = 3)

Table 11: *In vitro* release of febuxostat fast disintegrating tablets

Time (min)	FDT-1	FDT-2	FDT-3	FDT-4	FDT-5	FDT-6	FDT-7	FDT-8	FDT-9
0	0	0	0	0	0	0	0	0	0
5	15.54±0.87	23.42±1.24	34.52±0.62	30.40±0.87	35.41±1.03	37.42±0.32	35.10±0.69	39.22±1.3	38.42±1.0
10	23.14±0.62	34.41±1.03	46.72±1.24	37.52±1.31	45.90±1.00	58.10±1.00	54.52±1.00	60.45±0.45	62.54±0.21
15	32.72±0.89	46.51±0.79	57.42±0.79	53.85±1.03	54.80±0.28	68.54±.089	65.41±0.89	75.14±0.90	76.21±1.3
20	43.14±1.0	57.64±0.89	69.88±0.24	64.90±0.89	63.94±1.0	76.86±1.0	73.32±1.0	82.60±0.32	84.88±0.89
30	63.82±1.2	78.41±1.59	89.52±0.49	86.41±0.27	90.41±1.6	93.50±1.0	90.41±0.28	95.90±0.31	95.93±0.32

Data are expressed as mean ± S.D. (n = 3)

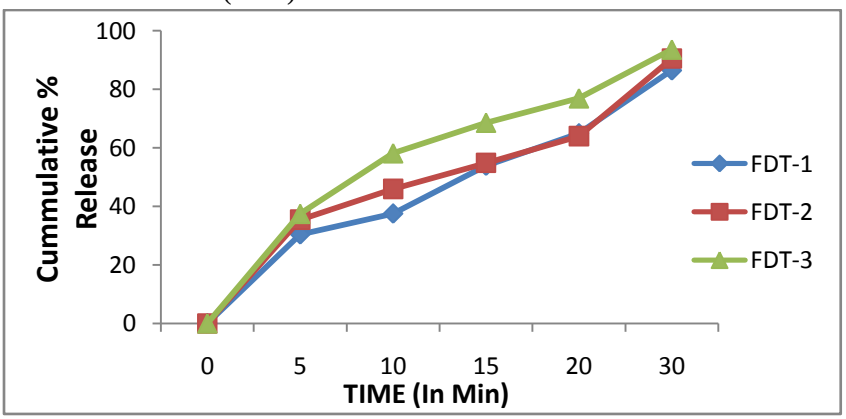

Figure 14: Percent release of febuxostat fast disintegrating tablets (FDT-1 - FDT-3)

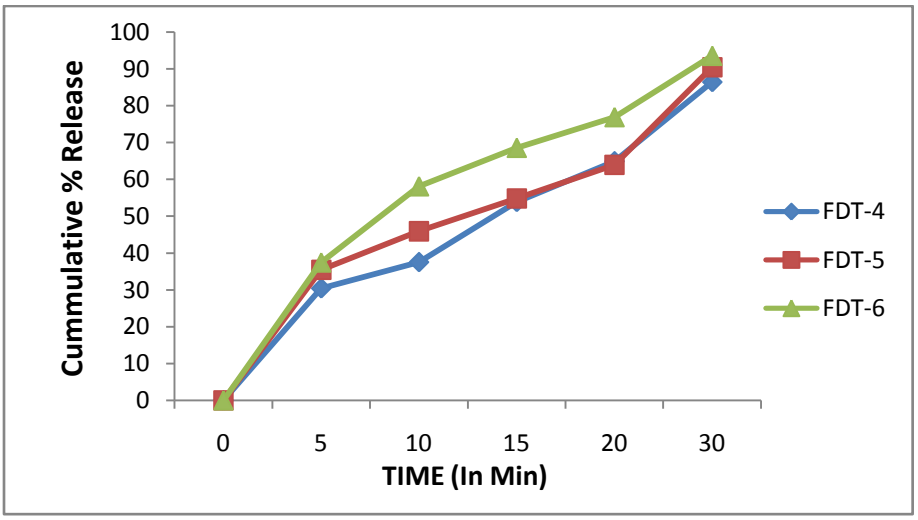

Figure 15: Percent release of febuxostat fast disintegrating tablets (FDT-4 - FDT-6)

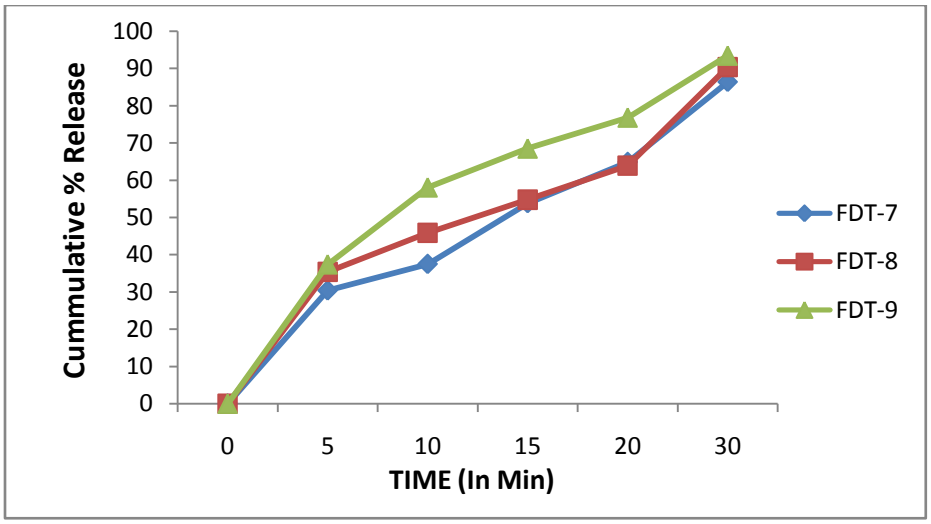

Figure 16: Percent release of febuxostat fast disintegrating tablets (FDT-7 – FDT-9)

Stability Studies

Selected formulation showed no significant variation in all the parameters under the test period i.e. Initial, 1 month, 2 months and 3 months at accelerated conditions i.e. $40^0 \pm 2^0$C and RH 75±5%. The results are shown in table 12.

Table 12: Effect of storage conditions on FDT-8 formulation

Time Period	Avg. weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Wetting Time (Sec)	D.T. (sec)	Drug Content (%)
Initial	249.7±1.41	3.03±0.040	5.17±0.094	25.41±1.41	31.41±1.45	100.50±0.43
1 month	249.5 ± 1.21	3.02±0.020	5.03±0.085	27.20±1.05	32.45±1.20	99.96±0.34
2 months	250.41±1.08	3.03±0.025	5.18±0.082	23.80±1.30	30.80±1.45	99.48±0.64
3 months	248.70±1.23	3.01±0.016	4.85±0.064	26.54±1.63	31.85±1.08	98.93±0.28

The similarity factor (F2) was calculated for the comparison of the dissolution profile before and after stability studies. The FDT-8 value was found to be 89.30 that were more than 50, indicating a close similarity between both

the dissolution profiles. Hence, the result of the stability studies confirmed that the developed formulation is very stable which can be seen in table 13.

Table 13: Comparison of Drug Release Data Before and After Storage

Time(min)	Percent Drug Released ± S.D.	
	Initial	After stability studies
0	0	0
5	39.22±1.3	40.14±0.56
10	60.45±.45	60.92±0.78
15	75.14±0.90	78.65±0.34
20	82.60±.32	80.44±0.63
30	95.90±.31	94.42±0.48

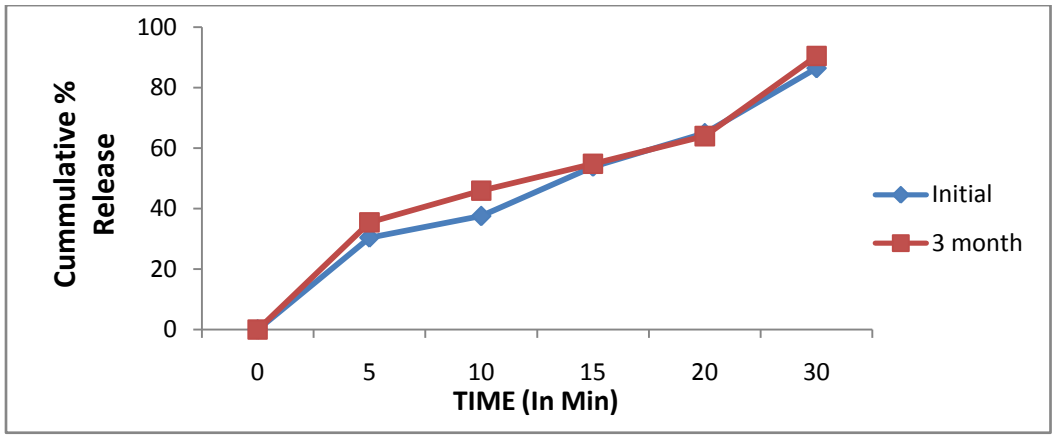

Figure 17: Comparison of drug release before and after stability studies

Table 14: Difference Factor and Similarity Factor

DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2) in OGD Media					
Time (t) [mins]	**Initial**	**3 Month**	**Rt-Tt**	**$(Rt-Tt)^2$**	**|Rt-Tt|**
5	39.22	40.14	-0.92	0.85	0.92
10	60.45	60.92	-0.47	0.22	0.47
15	75.14	73.65	1.49	2.22	1.49
20	82.6	80.44	2.16	4.67	2.16
30	95.9	94.42	1.48	2.19	1.48
Sum	**353.31**			**10.14**	**6.52**
	Number of Time points or intervals (Excluding Zero)				**6**
	Difference Factor - F1 [Acceptance Criteria : 0 - 15]				**1.85**
	Similarity Factor - F2 [Acceptance Criteria : 50 - 100]				**89.3**

Summary and Conclusion

Compounds with poor aqueous solubility are extremely challenging to be developed as new formulations. One of the pharmaceutical strategies to improve the oral bioavailability is the formulation of solid dispersions.

Febuxostat was selected as model drug for the research work because; Firstly, it has poor aqueous solubility and low dissolution rate, therefore it is necessary to increase the water solubility of the drug for therapeutic purpose. Secondly, febuxostat was chosen because of its better pharmacokinetic properties (low dose and longer half-life) that are well suited for its formulation as fast disintegrating tablets.

The preformulation studies of drug were carried out:

- Identification of the Drug
- Determination of absorption maxima (λ_{max}) and preparation of standard plots
- Drug – carrier compatibility studies

The model drug was formulated as a solid dispersion with β-CD by kneading method in order to improve the solubility and drug dissolution. Solid dispersions were characterized for solubility, *in vitro* drug release, FTIR, DSC studies. Among the different formulations containing febuxostat and β-CD, solid dispersions in 1:2 ratio (SD 2) revealed better solubility and dissolution rate and this formulation has been selected for the preparation of fast disintegrating tablets.

Formulation of fast disintegrating tablets of febuxostat was successfully carried out by direct compression technique using solid dispersions and superdisintegrants. The superdisintegrants used were synthetic (Crospovidone and CCM) as well as natural (Locust Bean Gum). The tablets were evaluated for their organoleptic (color, odor, taste), physical (size, shape and texture) and quality control parameters (diameter, thickness, hardness, friability, disintegration time, wetting time and dissolution studies). Based on these parameters and on further studies, the superdisintegrants i.e. Locust Bean Gum showed the better results in comparison to the crosspovidone and CCM.

The promising formulations (FDT-8) was selected for the stability studies at 40±2º C and 75±5 % RH for a period of 3 months. No significant changes in physical properties, drug content and drug release of the tablets were observed. The dissolution similarity factor was also calculated to compare before and after storage dissolution profile. The FDT-8 value was found to be more than 50 indicating a close similarity between both the dissolution profiles.

The fast disintegrating tablets of Antigout (Febuxostat) was found to be a better option in control of gout and hyperuricemia by way of fast onset of action by patient convenience and compliance.

References

1. Shekhar, R. S. (2012). Recent Trends of Oral Fast Disintegrating Tablets-An Overview of Formulation and Taste Masking Technology. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, *3*(1), 771-793.
2. Puttalingaiah, L., Kavitha, K., & Mani, T. (2011). Fast disintegrating tablets: An overview of formulation, technology and evaluation. *RJPBCS*, *2*(2), 589.
3. Fu, Y., Yang, S., Jeong, S. H., Kimura, S., & Park, K. (2004). Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *21*(6), 433–475.
4. Bandari, S., Mittapalli, R. K., Gannu, R., Rao, Y. M. (2008). Orodispersible tablets - An overview. *Asian J. Pharm.,* 2-11.
5. Giri, T. K., & Tripathi, D. K. (2010). Majumdar R. Formualtion aspects in the development of orodispersible tablets: An overview. *Int J Pharm Pharm Sci*., 2, 38-42.
6. Valia, K. H. (1999). Method for making fast melt tablets. US Patent 5,939,091.
7. Bonadeo, D., Ciccarello, F., & Pagano, A. (1998). Process for the preparation of a granulate suitable to the preparation of rapidly disintegratable mouth-soluble tablets and compositions obtained thereby. US Patent. 6,316,029.
8. Manivannan, R. (2005). Oral disintegrating tablets - A future compaction. *Int. J. Pharm. Res*. *Dev*., 1-10.
9. Allen, J., Loyd, V., & Wang, B. (1996). Process for making a particulate support matrix for making a rapidly dissolving tablet. US Patent 5,587,180.
10. Allen, J., Loyd, V., Wang, B., & Davis, L. D. 1998. Rapidly dissolving tablet. US Patent 5,807,576.
11. Amborn, J., Tiger, V. (2001). Apparatus for handling and packaging friable tablets. US Patent 6,311,462.
12. Bisht, M., & Bist, S. S. (2011). Febuxostat: a novel agent for management of hyperuricemia in gout. *Indian journal of pharmaceutical sciences*, *73*(6), 597-600.
13. Drug Bank of Febuxostat. (DB04854)